Amendments to the Claims:

This listing of claims will replace all prior versions, and listings of claims in the application:

Listing of Claims:

1 - 107. (cancelled)

108. (currently amended) A humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin and heavy and light chain variable region frameworks from acceptor immunoglobulin heavy and light chains, which humanized immunoglobulin specifically binds to an antigen with an affinity constant within about four-fold that of the donor immunoglobulin, wherein said humanized immunoglobulin comprises at least three amino acids from the donor immunoglobulin heavy chain framework outside the Kabat and Chothia CDRs that replace the corresponding amino acids in the acceptor immunoglobulin heavy chain framework, wherein each of these at least three donor amino acids:

(I) is immediately adjacent to one of the CDRs, or

(II) is capable of interacting with the CDRs, or

(III) is typical at its position for human immunoglobulin sequences, and the replaced amino acid is rare at its position for human immunoglobulin sequences.

109. (previously presented) A humanized immunoglobulin according to claim 108, wherein said humanized immunoglobulin binds to the antigen with an affinity constant of at least $10^8\ M^{-1}$.

110. (currently amended) A humanized immunoglobulin having a complementarity determining region from a donor immunoglobulin and heavy and light chain variable region frameworks from acceptor immunoglobulin heavy and light chains, which humanized immunoglobulin specifically binds to an antigen with an affinity constant within about four-fold that of the donor immunoglobulin, wherein said humanized immunoglobulin comprises at least three amino acids from the donor immunoglobulin heavy chain framework outside the Kabat

and Chothia CDRs that replace the corresponding amino acids in the acceptor immunoglobulin heavy chain framework, wherein each of these at least three donor amino acids:

(I) is immediately adjacent to one of the CDRs, or

(II) is capable of interacting with the CDRs

111. (previously presented) A humanized immunoglobulin according to claim 110, wherein said humanized immunoglobulin binds to the antigen with an affinity constant of at least 10^8 M^{-1}.

112. (currently amended) A humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin and heavy and light chain variable region frameworks from acceptor immunoglobulin heavy and light chains, which humanized immunoglobulin specifically binds to an antigen with an affinity constant within about four-fold that of the donor immunoglobulin, wherein said humanized immunoglobulin comprises at least three amino acids from the donor immunoglobulin heavy chain framework outside the Kabat and Chothia CDRs that replace the corresponding amino acids in the acceptor immunoglobulin heavy chain framework, and each of these said donor amino acids:

is capable of interacting with the CDRs.

113. (previously presented) A humanized immunoglobulin according to any one of claims 108 through 112, wherein said humanized immunoglobulin is an antibody tetramer, Fab, or (Fab')2.

114. (previously presented) A humanized immunoglobulin according to any one of claims 108 through 112, which is substantially pure.

115. (previously presented) A pharmaceutical composition comprising a humanized immunoglobulin according to claim 114 in a pharmaceutically acceptable carrier.

116. (currently amended) A humanized immunoglobulin comprising a complementarity determining region from a donor immunoglobulin and [[an]] heavy and light chain acceptor immunoglobulin variable region frameworks, which humanized immunoglobulin specifically binds to an antigen with an affinity constant within about four-fold that of the donor immunoglobulin, wherein the heavy and light chain acceptor immunoglobulin variable region frameworks [is] are [[a]] consensus frameworks from many human antibodies, and wherein said humanized immunoglobulin comprises amino acids from the donor immunoglobulin variable region framework outside the CDRs that replace the corresponding amino acids in the one or both of the heavy and light chain acceptor immunoglobulin variable region frameworks, wherein each of these said donor amino acids is capable of interacting with the CDRs.

117. (previously presented) A humanized immunoglobulin according to claim 116, wherein said humanized immunoglobulin binds to the antigen with an affinity constant of at least 10^8 M^{-1}.

118. (Cancelled)

119. (previously presented) A humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin and heavy and light chain variable region frameworks from acceptor immunoglobulin heavy and light chains, which humanized immunoglobulin specifically binds to an antigen with an affinity constant within about four-fold that of the donor immunoglobulin, wherein the acceptor immunoglobulin heavy chain variable region framework is a consensus of human immunoglobulin heavy chain variable region frameworks, and wherein said humanized immunoglobulin heavy chain comprises amino acids from the donor immunoglobulin framework outside the CDRs that replace the corresponding amino acids in the acceptor immunoglobulin framework, wherein each of these said donor amino acids is capable of interacting with the CDRs.

120. (previously presented) A humanized immunoglobulin according to claim 119, wherein said humanized immunoglobulin binds to the antigen with an affinity constant of at least 10^8 M^{-1}.

121. (Cancelled)

122. (currently amended) A humanized immunoglobulin according to any one of claims 116 through [[121]] 120, wherein said humanized immunoglobulin is an antibody tetramer, Fab, or (Fab')2.

123. (currently amended) A humanized immunoglobulin according to any one of claims 116 through [[121]] 120, which is substantially pure.

124. (previously presented) A pharmaceutical composition comprising a humanized immunoglobulin according to claim 123 in a pharmaceutically acceptable carrier.

125. (currently amended) A method of producing a humanized immunoglobulin that specifically binds to an antigen with an affinity constant within about four-fold that of the donor immunoglobulin, comprising the steps of:

(1) selecting an acceptor immunoglobulin heavy chain variable region framework whose sequence is a consensus sequence of human heavy chain variable region framework sequences;

(2) synthesizing a DNA segment encoding a humanized immunoglobulin heavy chain variable region, comprising complementarity determining regions (CDRs) from a donor immunoglobulin heavy chain variable region and the selected acceptor immunoglobulin heavy chain variable region framework;

(3) introducing a DNA segment encoding the humanized immunoglobulin heavy chain variable region and a DNA segment encoding a humanized immunoglobulin light chain variable region into a cell; and

(4) expressing the DNA segments in the cell to produce the humanized immunoglobulin.

126. (currently amended) The method of claim 125, further comprising the step of substituting an amino acid in the acceptor immunoglobulin heavy chain variable region framework outside the CDRs with the corresponding amino acid from the donor immunoglobulin heavy chain variable region, wherein the amino acid is capable of interacting with the CDRs.

127. (previously presented) The method of claim 125, further comprising the step of purifying the humanized immunoglobulin.

128. (previously presented) The method of claims 125 or 126, wherein said humanized immunoglobulin binds to the antigen with an affinity constant of at least 10^8 M^{-1}.

129. (currently amended) A method of producing a humanized immunoglobulin that specifically binds to an antigen with an affinity constant within about four-fold that of the donor immunoglobulin, the method comprising:

providing a cell containing DNA segments encoding humanized light and heavy chain variable regions; and expressing the DNA segments in the cell to produce the humanized immunoglobulin;

wherein the cell containing the DNA segments was produced by:

(1) selecting an acceptor immunoglobulin heavy chain variable region framework whose sequence is a consensus sequence of human immunoglobulin heavy chain variable region framework sequences;

(2) synthesizing a DNA segment encoding a humanized immunoglobulin heavy chain variable region, comprising a complementarity determining region (CDR) from a donor immunoglobulin heavy chain variable region and the selected acceptor immunoglobulin heavy chain variable region framework and further comprising amino acids from the donor immunoglobulin heavy chain framework outside the CDRs that replace the corresponding amino acids in the acceptor immunoglobulin heavy chain

variable region framework, at positions in the immunoglobulins where the amino acids are capable of interacting with the CDRs;

(3) introducing a DNA segment encoding the humanized immunoglobulin heavy chain variable region and a DNA segment encoding a humanized immunoglobulin light chain variable region into a cell.

130. (previously presented) The method of claim 129, further comprising the step of purifying the humanized immunoglobulin.

131. (previously presented) The method of claims 129 or 130, wherein said humanized immunoglobulin binds to the antigen with an affinity constant of at least 10^8 M^{-1}.

132. (previously presented) The method of claims 129 or 130, wherein said humanized immunoglobulin is an antibody tetramer, Fab, or (Fab')2.

133. (currently amended) A humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin and heavy and light chain variable region frameworks from acceptor immunoglobulin heavy and light chains, which humanized immunoglobulin specifically binds to an antigen with an affinity constant within about four-fold that of the donor immunoglobulin, wherein said humanized immunoglobulin comprises an amino acid from the donor immunoglobulin framework outside the CDRs that replaces the corresponding amino acid in the acceptor immunoglobulin frameworks, at a position selected from the group consisting of L9, L10, L13, L36, L41, L42, L48, L49, L63, L70, L71, L79, L87, L106, H37, H48, H49, H66, H67, H68, H72, H79, H81, H82b, H86, H87, H89, H91, H94, H103, H104, H105 and H107, utilizing the Kabat numbering system where the donor amino acid:

(I) is adjacent to a CDR in the donor immunoglobulin sequence, or
(II) is capable of interacting with the CDRs, or
(III) is typical at its position for human immunoglobulin sequences, and the replaced amino acid is rare at its position for human immunoglobulin sequences[[;]].

134. (previously presented) A humanized immunoglobulin according to claim 133, having three CDRs from the heavy chain of the donor immunoglobulin and three CDRs from the light chain of the donor immunoglobulin.

135. (previously presented) A humanized immunoglobulin according to claim 133, wherein said humanized immunoglobulin binds to the antigen with an affinity constant of at least 10^8 M^{-1}.

136. (Cancelled)

137. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position L9 has been replaced.

138. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position L10 has been replaced.

139. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position L13 has been replaced.

140. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position L36 has been replaced.

141. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position L41 has been replaced.

142. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position L42 has been replaced.

143. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position L48 has been replaced.

144. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position L49 has been replaced.

145. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position L63 has been replaced.

146. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position L70 has been replaced.

147. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position L71 has been replaced.

148. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position L79 has been replaced.

149. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position L87 has been replaced.

150. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position L106 has been replaced.

151. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position H37 has been replaced.

152. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position H48 has been replaced.

153. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position H49 has been replaced.

154. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position H66 has been replaced.

155. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position H67 has been replaced.

156. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position H68 has been replaced.

157. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position H72 has been replaced.

158. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position H79 has been replaced.

159. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position H81 has been replaced.

160. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position H82b has been replaced.

161. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position H86 has been replaced.

162. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position H87 has been replaced.

163. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position H89 has been replaced.

164. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position H91 has been replaced.166.

165. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position H94 has been replaced.

166. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position H103 has been replaced.

167. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position H104 has been replaced.

168. (previously presented) A humanized immunoglobulin according to claim 133, whercin the amino acid at position H105 has been replaced.

169. (previously presented) A humanized immunoglobulin according to claim 133, wherein the amino acid at position H107 has been replaced.

170. (previously presented) A humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin and heavy and light chain variable region frameworks from acceptor immunoglobulin heavy and light chains, which humanized immunoglobulin specifically binds to an antigen with an affinity constant within about four-fold that of the donor immunoglobulin, wherein said humanized immunoglobulin comprises an amino acid from the donor immunoglobulin framework outside the CDRs that replaces the corresponding amino acid in the acceptor immunoglobulin framework, at a position where the donor amino acid:

is adjacent to a CDR in the donor immunoglobulin sequence;

wherein said position is selected from the group consisting of H49, H66, H94, and H103, utilizing the Kabat numbering system.

171. (previously presented) A humanized immunoglobulin according to claim 170 having three CDRs from the heavy chain of the donor immunoglobulin and three CDRs from the light chain of the door immunoglobulin.

172. (previously presented) A humanized immunoglobulin according to claim 170, wherein said humanized immunoglobulin binds to the antigen with an affinity constant of at least 10^8 M^{-1}.

173. (cancelled)

174. (previously presented) A humanized immunoglobulin according to claim170, wherein the amino acid at position H49 has been replaced.

175. (previously presented) A humanized immunoglobulin according to claim 170, wherein the amino acid at position H66 has been replaced.

176. (previously presented) A humanized immunoglobulin according to claim 170, wherein the amino acid at position H94 has been replaced.

177. (previously presented) A humanized immunoglobulin according to claim 170, wherein the amino acid at position H103 has been replaced.

178. (previously presented) A humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin and heavy and light chain variable region frameworks from acceptor immunoglobulin heavy and light chains, which humanized immunoglobulin specifically binds to an antigen with an affinity constant within about four-fold that of the donor immunoglobulin, wherein said humanized immunoglobulin comprises an amino acid from the donor immunoglobulin light chain framework outside the CDRs that replaces the corresponding amino acid in the acceptor immunoglobulin light chain framework, at a position where the donor amino acid;

is capable of interacting with the CDRs.

179. (previously presented) A humanized immunoglobulin according to claim 178 wherein said position is selected from the group consisting of L36, L48, L49, L70, L71 and L87, utilizing the Kabat numbering system.

180. (previously presented) A humanized immunoglobulin according to claim 178 or 179 having three CDRs from the heavy chain of the donor immunoglobulin and three CDRs from the light chain of the donor immunoglobulin.

181. (previously presented) A humanized immunoglobulin according to claim 178 or 179, wherein said humanized immunoglobulin binds to the antigen with an affinity constant of at least 10^8 M^{-1}.

182. (cancelled)

183. (previously presented) A humanized immunoglobulin according to claim 178, wherein the amino acid at position L36 has been replaced.

184. (previously presented) A humanized immunoglobulin according to claim 178, wherein the amino acid at position L48 has been replaced.

185. (previously presented) A humanized immunoglobulin according to claim 178, wherein the amino acid at position L49 has been replaced.

186. (previously presented) A humanized immunoglobulin according to claim 178, wherein the amino acid at position L70 has been replaced

187. (previously presented) A humanized immunoglobulin according to claim 178, wherein the amino acid at position L71 has been replaced.

188. (previously presented) A humanized immunoglobulin according to claim 178, wherein the amino acid at position L87 has been replaced.

189. (previously amended) A humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin and heavy and light chain variable region frameworks from acceptor immunoglobulin heavy and light chains, which humanized immunoglobulin specifically binds to an antigen with an affinity constant within about four-fold that of the donor immunoglobulin, wherein said humanized immunoglobulin comprises an amino acid from the donor immunoglobulin heavy chain framework outside the CDRs that replaces the corresponding amino acid in the acceptor immunoglobulin heavy chain framework, at a position where the donor amino acid:

is capable of interacting with the CDRs[[.]];

wherein said position is selected from the group consisting of H37, H48, H67, H71 and H72, utilizing the Kabat numbering system.

190. (previously presented) A humanized immunoglobulin according to claim 189 having three CDRs from the heavy chain of the donor immunoglobulin and three CDRs from the light chain of the donor immunoglobulin.

191. (currently amended) A humanized immunoglobulin according to claim 189, wherein said humanized immunoglobulin binds to the antigen with an affinity constant of at least 10^8 M^{-1}.

192. (cancelled)

193. (previously presented) A humanized immunoglobulin according to claim 189, wherein the amino acid at position H37 has been replaced.

194. (previously presented) A humanized immunoglobulin according to claim 189, wherein the amino acid at position H48 has been replaced.

195. (previously presented) A humanized immunoglobulin according to claim 189, wherein the amino acid at position H67 has been replaced.

196. (previously presented) A humanized immunoglobulin according to claim 189, wherein the amino acid at position H71 has been replaced.

197. (previously presented) A humanized immunoglobulin according to claim 189, wherein the amino acid at position H72 has been replaced.

198. (previously presented) A humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin and heavy and light chain variable region frameworks from acceptor immunoglobulin heavy and light chains, which humanized

immunoglobulin specifically binds to an antigen with an affinity constant within about four-fold that of the donor immunoglobulin, wherein the acceptor immunoglobulin heavy chain variable region framework is a consensus sequence of human immunoglobulin heavy chain variable region frameworks, and wherein said humanized immunoglobulin comprises an amino acid from the donor immunoglobulin framework outside the CDR that replaces the corresponding amino acid in the acceptor immunoglobulin framework, at a position in the immunoglobulins where the donor amino acid:

(I) is adjacent to a CDR in the donor immunoglobulin sequence, or

(II) is capable of interacting with the CDRs.

199. (previously presented) A humanized immunoglobulin according to claim 198, wherein said position is selected from the group of L36, L48, L49, L70, L71, L87, H37, H48, H49, H66, H67, H71, H72, H94, and H103, utilizing the Kabat numbering system.

200. (previously presented) A humanized immunoglobulin according to claim 198 or 199 having three CDRs from the heavy chain of the donor immunoglobulin and three CDRs from the light chain of the donor immunoglobulin.

201. (previously presented) A humanized immunoglobulin according to claim 198 or 199 wherein said humanized immunoglobulin binds to the antigen with an affinity constant of at least 10^8 M^{-1}.

202. (cancelled)

203. (previously presented) A humanized immunoglobulin according to claim 198, wherein the amino acid at position H37 has been replaced.

204. (previously presented) A humanized immunoglobulin according to claim 198, wherein the amino acid at position H49 has been replaced.

205. (previously presented) A humanized immunoglobulin according to claim 198, wherein the amino acid at position H67 has been replaced

206. (previously presented) A humanized immunoglobulin according to claim 198, wherein the amino acid at position H71 has been replaced.

207. (previously presented) A humanized immunoglobulin according to claim 198, wherein the amino acid at position H94 has been replaced.

208. (previously presented) A humanized immunoglobulin according to any one of claims 133, 170, 178, 179, 189, 198 and 199 which is substantially pure.

209. (previously presented) A pharmaceutical composition comprising a humanized immunoglobulin according to claim 208 in a pharmaceutically acceptable carrier.